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ORIGINAL ARTICLE

Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies*

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ABSTRACT

Objective: The marketed doses of ibandronate, 150 mg once-monthly oral and 3 mg quarterly intravenous (IV) injection, produce greater increases in lumbar spine bone mineral density than treatment with the 2.5 mg oral daily dose. This meta-analysis assessed whether these doses also reduce fracture risk relative to placebo.

Study design and methods: Individual patient data from the intent-to-treat populations of the BONE, IV fracture prevention, MOBILE, and DIVA studies were grouped into three dose levels based on annual cumulative exposure (ACE), defined as the annual dose (mg) × bioavailability (0.6%, oral; 100%, IV) or placebo. Six key non-vertebral fractures (NVFs) (clavicle, humerus, wrist, pelvis, hip, and leg), all NVFs, and all clinical fractures were examined.

Results: This meta-analysis included 8710 patients. Cox proportional-hazards models estimated the adjusted relative risk (*RR*) for fracture with ibandronate versus placebo, and time to fracture was compared using log-rank tests. The high-dose group (ACE ≥ 10.8 mg) showed significant reductions in the adjusted *RR* of key NVFs (34.4%, $p = 0.032$), all NVFs (29.9%, $p = 0.041$), and clinical fractures (28.8%, $p = 0.010$) relative to placebo. The high-dose group also had significantly longer time to fracture versus placebo for key NVFs ($p = 0.031$), all NVFs ($p = 0.025$), and clinical fractures ($p = 0.002$). Study limitations included: not all studies were placebo-controlled; a limited number of baseline characteristics were available for multivariate analyses.

Conclusion: Ibandronate at dose levels of ACE ≥ 10.8 mg, which includes the marketed 150 mg once-monthly oral and 3 mg quarterly IV injection regimens, may provide significant non-vertebral and clinical fracture efficacy.

Introduction

The goal of osteoporosis treatment is the prevention of all fracture types, including both vertebral and non-vertebral fractures (NVFs)[1]. While vertebral fracture is the most common osteoporotic fracture type[2], NVFs, such as those of the hip, can be the most debilitating and costly[3,4]. Several clinical trials of oral bisphosphonates (BPs) (including alendronate, risedronate, and ibandronate) have shown that daily BP therapy increases bone mineral density (BMD), reduces bone turnover, and reduces the risk of fractures in women with

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postmenopausal osteoporosis (PMO)[5–8]. However, to our knowledge there have been no prospective studies examining the antifracture efficacy of approved weekly, monthly, or quarterly BP treatments.

Over the course of the ibandronate clinical development program, the frequency of dosing regimens was extended to include the 150 mg once-monthly oral and 3 mg quarterly intravenous (IV) injection regimens. In the BONE (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe) fracture trial, 2.5 mg daily oral treatment significantly increased lumbar spine (LS) BMD and reduced vertebral fracture risk (relative risk reduction = 52%, $p < 0.002$) in the overall population compared with placebo after 3 years of treatment[5]. In the overall study population, daily ibandronate therapy was not shown to reduce NVFs. However, the study was not designed with sufficient statistical power to examine NVFs as a secondary endpoint. In a post hoc analysis, daily ibandronate significantly reduced NVFs (relative risk reduction = 69%, $p = 0.0027$) in a higher-risk subgroup of women with baseline femoral neck (FN) BMD T-score < –3.0[9]. Subsequent clinical trials of the oral 150 mg once-monthly and 3 mg quarterly injection ibandronate regimens have demonstrated greater BMD increases than those seen with the daily regimen. In the Monthly Oral iBandronate In LadiEs (MOBILE) trial, women receiving 150 mg once-monthly oral ibandronate exhibited significantly greater increases in BMD at the LS ($p < 0.001$), total hip (TH) ($p < 0.05$), FN ($p < 0.05$), and trochanter (TR) ($p < 0.05$) after 2 years compared with the 2.5 mg daily oral ibandronate study arm[10]. Similarly, in the Dosing IntraVenous Administration (DIVA) trial, women receiving 3 mg quarterly ibandronate IV injection showed significantly greater increases in BMD at the LS, TH, and TR after 2 years compared with women receiving the 2.5 mg daily oral regimen ($p < 0.001$ for all three sites)[11].

It has been suggested that administration of a BP with a dosing regimen less frequent than weekly requires a higher dose than the total dose of daily drug[12]. The higher dosing regimens examined in the DIVA and MOBILE studies were designed to provide improved efficacy with monthly oral and quarterly IV administration. Thus, the significant gains in BMD observed with the 150 mg oral monthly and 3 mg quarterly IV injection dosing regimens compared with the 2.5 mg daily dose were anticipated, given that these doses represent a twofold increase in annual drug exposure relative to the daily dose.

Considering both the increase in dose level and the significantly larger increases in BMD achieved with the 150 mg once-monthly oral and 3 mg quarterly IV injection ibandronate regimens compared with the 2.5 mg daily oral regimen, it was hypothesized that these dosages may also provide greater reductions in NVF risk. A recent meta-analysis by Cranney *et al.*, which pooled data from the DIVA and MOBILE studies, compared annual cumulative exposure (ACE) ≥ 10.8 mg with ACE < 7.2 mg or ACE = 5.5 mg. Ibandronate ACE ≥ 10.8 mg was found to be significantly more effective at reducing NVF than either of the lower ACEs examined[13].

Across the BONE, IV fracture prevention[14], MOBILE, and DIVA trials, it was observed that similar ACEs resulted in similar gains in BMD. Considering the similarities in the patient populations, it was possible to pool data from these four studies[9–11,14,15]. The studied doses have also been shown to be well tolerated in clinical trials[5,10,11,14]. Our meta-analysis of four ibandronate studies examined fracture risk reduction over a wider range of ibandronate dosages compared with the Cranney analysis and investigated whether the higher ibandronate doses (including the 150 mg oral monthly and 3 mg quarterly IV injection regimens) would also provide greater NVF and clinical fracture protection versus placebo.

Patients and methods

Study design

In this meta-analysis, individual patient data from the four phase III clinical trials of ibandronate in women with PMO and at least 2 years of follow-up for fractures were combined and analyzed. These four studies represent the largest and most relevant prospective randomized, double-blind clinical trials of ibandronate, including BONE[5], the IV fracture prevention study[14], MOBILE[10,16], and DIVA[11,15]. The dosing regimens utilized in these studies are summarized in Table 1. Earlier small phase II studies of shorter duration, including dose-ranging studies, were not included in the analysis due to substantial differences in study size, populations, and study duration.

All of the included trials were treatment studies with similar study populations – women 55–80 years of age with PMO – and similar inclusion criteria, with a few exceptions noted below. All four trials had identical procedures for ascertainment of NVFs, including collection of NVFs as adverse events and mandatory X-ray confirmation. The BONE and the IV fracture prevention studies were placebo-controlled 3-year fracture endpoint trials that examined vertebral fractures as the primary endpoint. Inclusion criteria for the BONE and the IV fracture prevention studies required one to four prevalent vertebral fractures and low LS BMD T-score (–2.0 to –5.0). The MOBILE and DIVA studies were active-controlled 2-year BMD

Table 1. *Dose level, ACE, and sample size by trial and treatment regimen*

Dose level ACE group, mg (*n* for group)	Ibandronate regimen	ACE, mg	Sample size				
			BONE	IV Fracture	MOBILE	DIVA	Total
High dose ACE ≥ 10.8 (*n* = 1290)	3 mg IV q 3 mo*	12.0	–	–	–	459	459
	2 mg IV q 2 mo	12.0	–	–	–	440	440
	150 mg PO/mo*	10.8	–	–	391	–	391
Mid dose ACE = 5.5–7.2 (*n* = 3585)	100 mg PO/mo	7.2	–	–	392	–	392
	50 + 50 mg PO/mo†	7.2	–	–	391	–	391
	20 mg PO int‡	5.8	976	–	–	–	976
	2.5 mg PO/day*	5.5	977	–	392	457	1826
Low dose ACE = 2–4 (*n* = 1911)	1.0 mg IV q 3 mo	4.0	–	961	–	–	961
	0.5 mg IV q 3 mo	2.0	–	950	–	–	950
Placebo ACE = 0 (*n* = 1924)	Placebo	0.0	975	949	–	–	1924
	Total, *n*		2928	2860	1566	1356	8710

*US Food and Drug Administration approved marketed doses
†50 mg of ibandronate given on two consecutive days
‡Intermittent: 20 mg every other day × 12 doses q 3 mo
ACE = annual cumulative exposure in mg, calculated as annual dose times bioavailability (0.6% oral, 100% IV)
BONE = oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe[5]; DIVA = Dosing IntraVenous Administration[11,15]; IV = intravenous; IV Fracture = the IV fracture prevention study[14]; MOBILE = Monthly Oral iBandronate In LadiEs[10,16]; PO = oral

studies that examined percent change in LS BMD as the primary endpoint. MOBILE and DIVA were of identical design, ran concurrently, and had the same inclusion criteria and active comparator (ibandronate 2.5 mg oral daily); however, they had different dosing regimens and routes of administration (oral versus IV injection). Additionally, inclusion criteria for MOBILE and DIVA did not require prevalent vertebral fractures but they did require low LS BMD T-score (–2.5 to –5.0). Patients in all studies received daily supplements of vitamin D (400 IU) and calcium (500 mg).

Dose groups and ACE

To calculate ACE, the drug dose (mg) was multiplied by the total number of annual doses and by an absorption factor (0.6% for oral[17] and 100% for IV). Patients were then grouped into one of three dose levels based on ACE: high (≥ 10.8 mg), mid (5.5–7.2 mg), and low (2.0–4.0 mg) (Table 1) or placebo. The 150 mg oral once-monthly and 3 mg IV quarterly are both approved, marketed dosages and fall within the high-dose group. The 2.5 mg daily approved dose fell within the low-ACE group.

Assessments

The primary endpoint was key NVFs (clavicle, humerus, wrist, hip, pelvis, leg) as defined in previous BP trials[6,8]. All NVFs and all clinical fractures (a category that includes all NVFs and symptomatic vertebral fractures) were also examined. All NVFs included all non-spine fractures except fractures of the skull, fingers, and toes, which are not generally considered osteoporotic. In all four clinical trials, NVFs and clinical fractures were recorded as adverse events, and confirmation of fractures by radiographs was mandatory. X-rays of NVFs were confirmed locally for all four studies. X-rays for clinical vertebral fractures were assessed centrally for the BONE and the IV fracture prevention studies, and locally for MOBILE and DIVA. Morphometric vertebral fractures were assessed only in the BONE and IV fracture prevention studies and were not available for this analysis.

Statistical methods

The analysis population included all patients in the intent-to-treat (ITT) populations who received at least one dose of ibandronate or placebo. The inclusion of the ITT populations rather than the per-protocol populations provided a broader population for analysis and constituted a more conservative approach to the assessment of treatment efficacy.

Cox regression models were used to determine the relative risk (hazard ratio [HR]) for key NVFs, all NVFs, and all clinical fractures for participants receiving ibandronate high-, mid-, and low-dose regimens compared with placebo. Cox models examined fracture risk using both 2-year and all-year data (BONE and the IV fracture prevention study were 3-year trials and MOBILE and DIVA were 2-year trials). The all-year data set included data from all available study years and the 2-year data set comprised only the first 2 years

of these four studies. Including data from all available study years maximized patient data, increasing the sample size and hence the statistical power of the analysis. Data were adjusted to account for potential differences in baseline patient characteristics, including age, history of previous fracture, and baseline BMD T-score (LS or TH), across the four studies. Models assessing key NVFs and all NVFs were adjusted for TH BMD T-score. Models assessing all clinical fractures, which include both NVFs and clinical vertebral fractures, were adjusted for either LS or TH BMD T-score.

Kaplan–Meier analyses were used to investigate the time to fracture for the different ibandronate ACE groups; the log-rank test was used to assess statistical differences between the groups relative to placebo. The 2-year fracture rates were also determined by tabulating the proportion of patients at 2 years with at least one key NVF, any NVF, or any clinical fracture. This analysis was repeated using data from all study years.

Results

This analysis included 8710 patients from the ITT populations of the four clinical trials. Baseline characteristics were similar across trials (Table 2) except for age and baseline LS BMD T-score. The average age was slightly higher in the BONE and IV fracture prevention trials compared with the DIVA and MOBILE trials. Baseline mean LS T-scores were lower

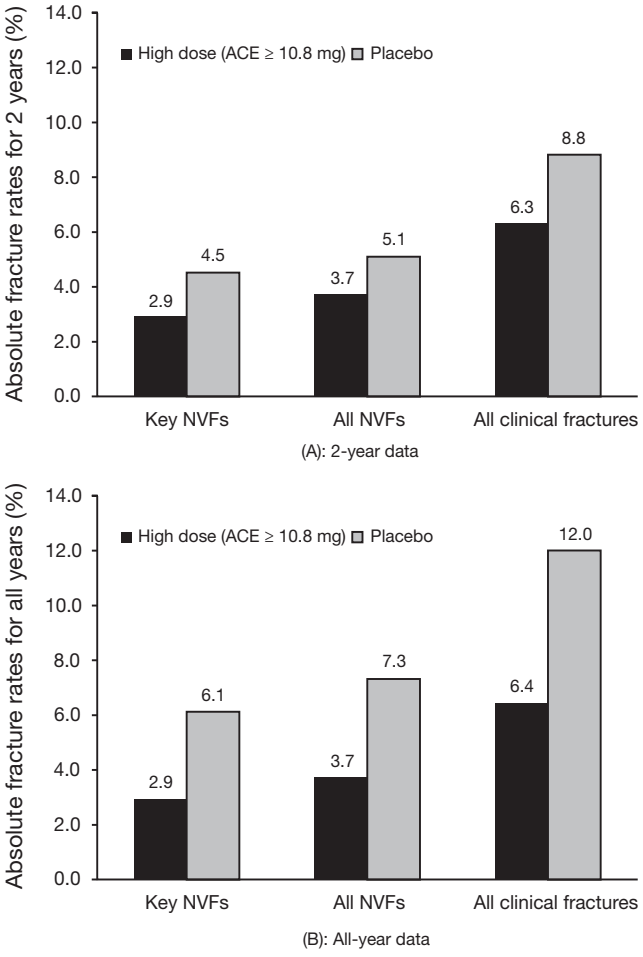

Figure 1. *Absolute fracture rates for key NVFs, all NVFs, and all clinical fractures at 2 years (A) and all years (B). ACE = annual cumulative exposure; NVFs = non-vertebral fractures*

Table 2. *Summary of baseline patient characteristics*

Baseline patient characteristic	IV Fracture MF4380 (*n* = 2860)	BONE MF4411 (*n* = 2928)	MOBILE BM16549 (*n* = 1566)	DIVA BM16550 (*n* = 1356)
Age, years, mean ± SD	66.97 ± 5.08	68.72 ± 6.15	66.01 ± 6.59	65.95 ± 6.17
Years since menopause, mean ± SD	19.33 ± 7.12	20.83 ± 7.92	18.57 ± 8.37	18.6 ± 8.02
Height, cm, mean ± SD	160.29 ± 5.91	160.03 ± 6.08	157.46 ± 6.58	158.16 ± 6.64
Weight, kg, mean ± SD	64.60 ± 9.12	66.68 ± 11.03	63.96 ± 11.33	64.02 ± 10.79
Body mass index, kg/m^2, mean ± SD	25.14 ± 3.25	26.04 ± 4.12	25.81 ± 4.38	25.62 ± 4.22
Smoker, *n* (%)	586 (20.49)	482 (16.46)	244 (15.58)	228 (16.81)
Clinical fracture, *n* (%)	1554 (54.34)	1666 (56.9)	733 (46.81)	586 (43.22)
Prevalent vertebral fracture, *n* (%)	2814 (98.43)	2742 (93.68)	na	na
BMD T-score, mean ± SD				
Lumbar spine	–2.81 ± 0.88	–2.74 ± 0.86	–3.28 ± 0.59	–3.26 ± 0.57
Total hip	–1.84 ± 0.81	–1.73 ± 0.86	–1.81 ± 0.85	–1.95 ± 0.87
Femoral neck	–2.13 ± 0.81	–2.03 ± 0.88	–2.11 ± 0.77	–2.14 ± 0.72
Trochanter	–1.53 ± 0.83	–1.38 ± 0.92	–1.51 ± 0.84	–1.51 ± 0.8

BMD = bone mineral density; BONE = oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe[5]; DIVA = Dosing IntraVenous Administration[11,15]; IV = intravenous; IV Fracture = the IV fracture prevention study[14]; MOBILE = Monthly Oral iBandronate In LadiEs[10,16]; na = not applicable; SD = standard deviation

Table 3. *Adjusted hazard ratios for fractures with ibandronate treatment at varying ACE levels compared with placebo, controlled for age, baseline total hip BMD (unless otherwise noted), and fracture history*

Fracture type	All-year models			2-year models		
ACE group (mg)	Adjusted hazard ratio	95% CI	*p*-value	Adjusted hazard ratio	95% CI	*p*-value
Key non-vertebral sites*						
High† (≥ 10.8)	0.656	0.45–0.96	0.032‡	0.717	0.48–1.08	0.108
Mid§ (5.5–7.2)	1.15	0.90–1.46	0.270	1.23	0.93–1.64	0.153
Low†† (≤ 4.0)	0.871	0.66–1.15	0.334	0.929	0.66–1.31	0.676
All non-vertebral						
High† (≥ 10.8)	0.701	0.50–0.99	0.041‡	0.729	0.51–1.04	0.083
Mid§ (5.5–7.2)	1.04	0.83–1.30	0.722	1.06	0.82–1.38	0.650
Low†† (≤ 4.0)	0.893	0.69–1.15	0.383	0.869	0.64–1.18	0.373
All clinical						
High† (≥ 10.8)	0.730	0.56–0.95	0.019‡	0.706	0.54–0.93	0.013‡
Mid§ (5.5–7.2)	0.916	0.77–1.09	0.330	0.877	0.72–1.08	0.206
Low†† (≤ 4.0)	0.821	0.67–1.00	0.055	0.761	0.60–0.97	0.028‡
All clinical¶						
High† (≥ 10.8)	0.712	0.55–0.92	0.010‡	0.693	0.53–0.91	0.008‡
Mid§ (5.5–7.2)	0.881	0.74–1.05	0.148	0.843	0.69–1.03	0.087
Low†† (≤ 4.0)	0.887	0.73–1.07	0.211	0.801	0.64–1.00	0.055

*Includes clavicle, humerus, wrist, pelvis, hip, and leg
†150 mg monthly oral, 3 mg quarterly IV, and 2 mg q 2 mo IV
‡Significance defined as $p < 0.05$ (unadjusted for multiple comparisons)
§Includes 2.5 mg daily oral, 20 mg oral intermittent, 2 × 50 mg monthly oral, 100 mg monthly oral
††Includes 0.5 mg IV q 3 mo and 1.0 mg IV q 3 mo
¶Cox models adjusted for lumbar spine BMD
ACE = annual cumulative exposure; BMD = bone mineral density; CI = confidence interval; IV = intravenous

for patients in the MOBILE (–3.28) and DIVA (–3.26) trials compared with the BONE (–2.74) and IV fracture prevention (–2.81) trials, indicating that these patients had more severe osteoporosis at the spine. However, baseline BMD T-scores at the TH, FN, and TR (as well as absolute values) were comparable among the four clinical trials. Absolute fracture rates from this analysis are shown in Figure 1.

Risk of fracture

Cox proportional-hazards regression models were used to control for differences in patient baseline characteristics in the four trials. Adjusted HRs for fractures for patients receiving ibandronate compared with placebo are shown in Table 3. For models of all-year data, statistically significant reductions in the risk of key NVFs, all NVFs, and all clinical fractures were observed for the high-ACE group (ACE ≥ 10.8 mg), which included the 150 mg once-monthly oral and 3 mg quarterly IV regimens, compared with placebo: 34.4% (HR = 0.656; 95% confidence interval [CI], 0.45–0.96; $p = 0.032$), 29.9% (HR = 0.701; 95% CI, 0.50–0.99; $p = 0.041$), and 28.8% (HR = 0.712; 95% CI, 0.55–0.92; $p = 0.010$), respectively. Similar trends in fracture risk reduction were seen with the 2-year models, despite a lower number of fractures and less statistical power than the all-year models. Statistical significance was achieved by the high-ACE group versus placebo for clinical fractures. Reductions in fracture risk for the low- and mid-ACE groups compared with placebo did not reach statistical significance for most of the fracture types examined, with the exception of the low-dose group in all clinical fracture models adjusted for TH BMD. Results of Cox models for all clinical fractures adjusted for either TH BMD or LS BMD were similar.

Time to fracture

The cumulative rates of fracture for study participants receiving ibandronate ACE ≥ 10.8 mg or placebo are shown for key NVFs (Figure 2), all NVFs (Figure 3), and all clinical fractures (Figure 4). The high-dose group (ACE ≥ 10.8 mg) had a significantly longer time to fracture versus placebo for key NVFs ($p = 0.031$), all NVFs ($p = 0.025$), and all clinical fractures ($p = 0.002$) at 2 years. When time to fracture for ACE < 10.8 mg was compared with placebo at 2 years, statistical significance was reached only for the all clinical fractures analysis ($p = 0.017$). Results of all-

year Kaplan–Meier analyses for the high-dose group were similar to the results of the 2-year analyses. All-year analyses for ACE < 10.8 mg did not reach statistical significance.

Discussion

The approved 150 mg once-monthly oral and 3 mg quarterly IV (ACE ≥ 10.8 mg) ibandronate dosing regimens provide an approximately twofold increase in dose and significantly larger gains in BMDs compared with the approved 2.5 mg daily oral regimen (ACE = 5.5 mg). In this analysis, data from the four phase III clinical trials of ibandronate, which included women of comparable age with PMO, were pooled to determine whether higher dose levels (ACE ≥ 10.8 mg) were also associated with reduced fracture risk compared with placebo. The ibandronate high-dose group (ACE ≥ 10.8 mg) demonstrated statistically significant fracture risk reductions in Cox regression models of data from all study years compared with placebo for key NVFs, all NVFs, and all clinical fractures (risk reductions of 34.4%, 29.9%, and 28.8%, respectively). In addition, time to fracture for key NVFs, all NVFs, and all clinical fractures was significantly longer for patients receiving the high doses of ibandronate (ACE ≥ 10.8 mg) compared with placebo.

Results of BP clinical trials attempting to demonstrate NVF risk reduction have been inconsistent[6–8,18,19]. NVF efficacy has been difficult to demonstrate in randomized clinical trials of BPs for a number of reasons, including low NVF fracture rates[20] and the role of non-skeletal risk factors (such as risk of falling and poor vision[21]) in NVF events. Additionally, most trials evaluate vertebral fractures as the primary endpoint, as this is required by regulatory agencies[22]. Consequently, most trials are not adequately statistically powered to show reductions in NVFs[21]. As a consequence of the difficulties associated with conducting clinical trials to assess NVF efficacy[20], meta-analyses and pooled analyses have been utilized to evaluate NVF risk reduction with daily BPs[13,23–26]. At this time, the efficacy of any weekly or monthly BP treatment in reducing fracture risk has not been prospectively evaluated in clinical trials.

The approximately 30–34% reduction in key NVF and all NVF risk achieved with ibandronate in our analysis is comparable to that reported for other BPs. Meta-analyses for daily alendronate have reported NVF relative risk reductions varying from 14% to 49%[23,27,28] and meta-analyses for daily risedronate have reported NVF relative risk reductions of 19–59%[23–26]. The vertebral and NVF efficacies of dosing regimens other than daily for alendronate and risedronate have not been assessed.

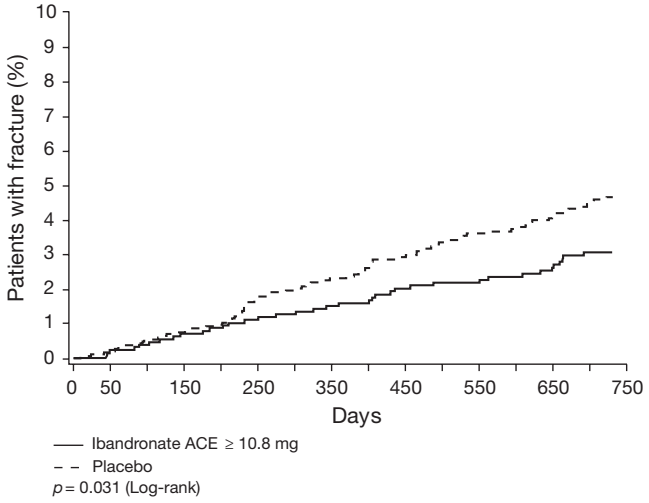

Figure 2. *Incidence of key non-vertebral fractures at 2 years in participants receiving ibandronate annual cumulative exposure (ACE) ≥ 10.8 mg or placebo*

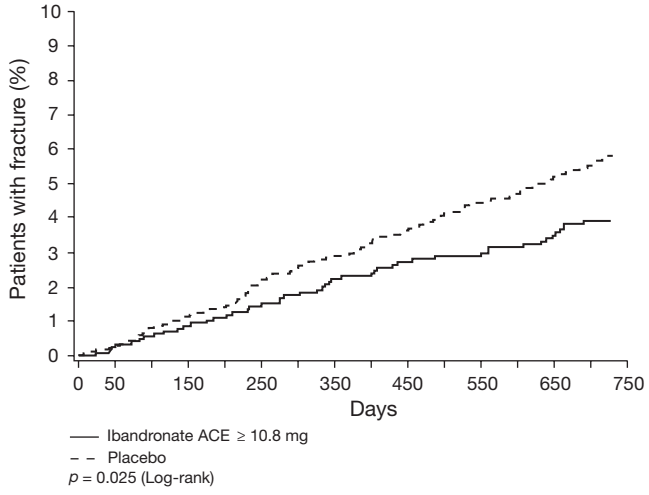

Figure 3. *Incidence of all non-vertebral fractures at 2 years in participants receiving ibandronate annual cumulative exposure (ACE) ≥ 10.8 mg or placebo*

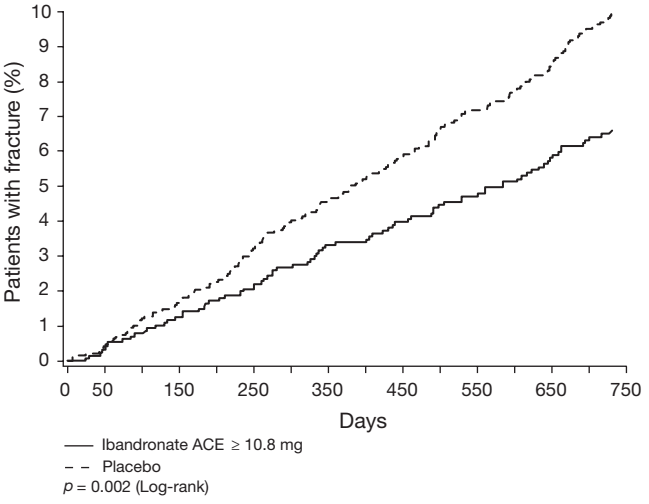

Figure 4. *Incidence of all clinical fractures at 2 years in participants receiving ibandronate annual cumulative exposure (ACE) ≥ 10.8 mg or placebo*

This meta-analysis examining the effect of ibandronate doses provides the first evidence for a statistically significant reduction in the risk of key NVFs, all NVFs, and clinical fractures for an approved oral BP with an extended dosing regimen. Our findings build upon the results of a meta-analysis recently presented by Cranney *et al.*, which evaluated 2-year data from the ibandronate DIVA and MOBILE trials[13]. In the Cranney meta-analysis, the relative risk of NVFs (defined as fractures of the clavicle, humerus, wrist, hip, pelvis, and leg) was reported to be reduced by 38% (HR = 0.620; 95% CI, 0.40–0.97; $p = 0.04$) with ibandronate high doses (ACE ≥ 10.8 mg, including the marketed 150 mg once-monthly and 3 mg IV quarterly regimens, and the 2 mg IV bimonthly unlicensed regimen) compared with ibandronate ACE = 5.5 mg (ACE for the 2.5 mg daily oral regimen).

Safety information for the ibandronate ACEs used in this meta-analysis has been previously reported[5,10,14,29]. Generally, both oral and IV ibandronate have been reported to be well tolerated. In the BONE trial, the 2.5 mg daily and 20 mg intermittent (administered every other day for 12 doses quarterly) oral regimens were well tolerated and had safety profiles similar to placebo. The frequency of upper gastrointestinal (GI) adverse events, which are of particular interest for oral BPs, was found to be similar among the placebo, daily, and intermittent regimens (27%, 25%, and 25%, respectively). In MOBILE[10], study doses ranged from 2.5 mg daily to 150 mg monthly oral. The incidence of treatment-related adverse events was low and comparable across all regimens. The incidence of upper GI adverse events was similar across treatment arms: 18%, 15.9%, 21.7%, and 16.9% in the 2.5 mg daily, 50 mg/50 mg (single doses on two consecutive days) monthly, 100 mg monthly, and 150 mg monthly arms, respectively.

Regarding the safety profile of IV ibandronate, the IV fracture prevention study reported that the 1 mg and 0.5 mg quarterly IV injections were well tolerated and the incidence of serious adverse events was similar to placebo (27%, 23%, and 25% for placebo, 1 mg, and 0.5 mg injections, respectively)[14]. In the DIVA trial, which tested higher dosages of IV ibandronate, the safety profiles of the 2 mg every 2 months and 3 mg quarterly IV regimens were comparable to the daily oral regimen. The rates of adverse events (85.3–88.6%), drug-related adverse events (36.8–46.4%), and drug-related adverse events leading to withdrawal (6.0–7.7%) were similar across treatment arms[30]. The number of drug-related serious adverse events was low and similar (0.4–1.1%, $n = 11$) across treatment arms[31].

The only other trial of extended-dose BP to report NVF data is the 3-year Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial[32], which examined NVFs and clinical fractures as secondary efficacy endpoints. The annual infusion of zoledronic acid reduced the risk of NVFs by 25% ($p < 0.001$) and clinical fractures by 33% versus placebo ($p < 0.001$ for both).

One strength of our analysis is the use of individual patient data, which allows examination of the time to fracture data and adjustment for patient-level covariates. The use of individual patient data is recognized as the ideal approach to the meta-analysis of clinical trials[33,34]. The large sample size provided by this meta-analysis increased the power to detect real differences in low fracture rates. The use of the ITT population is also optimal in osteoporosis clinical trials[35]. The four trials included in this meta-analysis were all large, well controlled, randomized, double-blind studies with similar study populations. Together, the studies had varying doses, which afforded the opportunity to address a predefined hypothesis that was based on a biologically plausible dose–response relationship. Finally, the primary endpoint of key NVFs was ascertained by identical criteria and procedures across the four trials.

There were a few important potential limitations of this analysis which should be mentioned. Not all of the studies included were placebo-controlled; the placebo fracture rates were derived from the two 3-year studies, whereas active-treatment fracture rates were derived from all four studies. We pooled patients within dose groups and compared fracture rates across trials compared with placebo. History of clinical fracture was used as a covariate in the Cox regression models. Baseline morphometric vertebral fracture data were not collected in all of the trials. A limited number of baseline patient characteristics were available for use in multivariate models. Although baseline characteristics were very similar across the trials and multivariate analyses controlled for key baseline differences that did exist, it is possible that there were other measured or unmeasured confounders. Accounting for such confounders (such as differences in study populations, designs, or implementation) could result in higher or lower estimates of the influence of ibandronate dose; however, there are no apparent reasons for a systematic directional bias in the results.

While randomized clinical trials are preferred for demonstrating NVF fracture risk reduction, they are difficult to conduct because they require large numbers of patients and a long duration, and they are expensive[20]. Additionally, ethical concerns have been raised over the use of placebo-controlled trials[36,37]. Despite the limitations, the findings of this meta-analysis provide valuable information to clinicians and suggest that ibandronate administered orally once

monthly at 150 mg and by IV injection once every 3 months at 3 mg provides reduced NVF and clinical fracture risk.

Conclusions

This study is the first to demonstrate NVF and clinical fracture risk reduction by a BP with a weekly, monthly, or quarterly dosing regimen for the treatment of PMO. In this meta-analysis, the high-dose level of ibandronate (ACE ≥ 10.8 mg), which includes the marketed doses of 150 mg once-monthly by mouth and 3 mg quarterly by IV injection, was associated with significant reductions in the risk of key NVFs, all NVFs, and clinical fractures (risk reductions of 34.4%, 29.9%, and 28.8%, respectively).

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